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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,072	01/25/2002	Genoveffa Franchini	15280-4003US	1664

7590 08/25/2005

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EXAMINER

PARKIN, JEFFREY S

ART UNIT	PAPER NUMBER
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1648

DATE MAILED: 08/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/048,072

Applicant(s)

FRANCHINI ET AL.

Examiner

Jeffrey S. Parkin, Ph.D.

Art Unit

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 03 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 May 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 and 12-17 is/are pending in the application.
- 4a) Of the above claim(s) 4 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,5-10 and 12-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 05192005.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

Serial No.: 10/048,072
Applicants: Franchini, G., et al.

Docket No.:15280-4003US
Filing Date: 01/25/02

Detailed Office Action

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the communication filed 19 May, 2005. Claim 4 has been withdrawn from further consideration by the examiner, pursuant to 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention. Claims 1-3, 5-10, and 12-17 are currently under examination.

Claim Objections

Claims 1-3, 5-10, and 12-17 are objected to because of the following informalities: it is generally recognized in the art that viral gene products are capitalized (e.g., the Gag, Env, Pol, or Nef proteins) whereas the viral genes themselves are italicized (e.g., the *gag*, *pol*, *env*, or *nef* genes) to avoid any confusion or ambiguity. Appropriate correction is required.

35 U.S.C. § 112, Second Paragraph

The previous rejection of claims 1-10 and 12-17 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is hereby withdrawn in response to applicants' arguments and amendment.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it

is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-3, 5-10, and 12-17 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The amended claims are broadly directed toward the administration of a human HIV-1 CTL recombinant viral vaccine encoding different HIV structural immunogens (e.g., Gag, gp120, Nef, or Pol). Additional limitations specify when the vaccine should be administered to the individual (e.g., viral load of less than 10,000 copies/ml). The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986).

As previously set forth, the courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide any guidance pertaining to the correlates of human protection. To date, it is not clear what type of immune response is required to provide a therapeutic benefit. What is the nature and specificity of the titer of the immune response required to provide an salubrious outcome? The disclosure is silent concerning this critical area.

2) HIV vaccines frequently fail because of the *quasispecies* nature of HIV infection. The plasticity of the HIV-1 genome and its contribution to immune escape are salient factors that have prevented the development of an effective vaccine. HIV-1 exists as a large pool of genotypically and phenotypically distinct isolates. It has been well-documented that the virus relies upon this heterogeneity to escape immune surveillance and detection. For instance, the majority of the neutralizing antibody response is directed toward a molecular determinant (V3) that undergoes rapid mutation. Thus, even when a neutralizing antibody or CD8+ response is generated, it rapidly becomes ineffective as other members of the *quasispecies* quickly replicate and grow out. The disclosure fails to provide any data addressing this concern.

3) The disclosure fails to provide sufficient guidance pertaining to those immunogens that are capable of conferring protection. The claims are broadly directed toward any recombinant viral vaccine encoding a peptides obtained from the Gag, Pol, Env, or Nef proteins. However, the disclosure fails to provide any guidance pertaining to the molecular determinants modulating protective immune responses. Which CTL epitopes are capable of stimulating a protective or therapeutic immune response of the proper specificity, titer, and duration?

4) The disclosure fails to provide any working embodiments. The only human example is purely prophetic and fails to set forth any meaningful data. Some data was provided from the macaque model,

however, this model is not an art-recognized model for vaccine development. Although animal models, such as the macaque system, are capable of providing important information pertaining to the understanding of pathogenesis and immunity, the results from such studies cannot be directly extrapolated to a clinical setting due to the structural differences between SIV and HIV.

5) The state-of-the-art vis-à-vis HIV CTL vaccine development is one of unpredictability (Haynes et al., 1996; Burton and Moore, 1998; Moore and Burton, 1999; Desrosiers, R., 2004). To date, there is not one single effective HIV vaccine on the market. Several clinical trials have been conducted but in every situation, the immunogen failed to induce a long-lasting and high-titer immune response. Common problems encountered with vaccine development include the extraordinary variability, or *quasispecies* nature, of HIV, the lack of an exact animal model of HIV-induced AIDS, and the lack of understanding of the correlates of protective immunity. The disclosure fails to address these concerns.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Applicants traverse and submit that they need not disclose every CTL epitope or peptide to practice the claimed invention. Applicants are reminded that the claims are directed toward a **vaccine** that induces an HIV-1-specific CD8⁺ response. Accordingly, there is an expectation that any given peptide employed in the claimed assay must be protective or therapeutic. Simply identifying a CTL epitope does not mean that it is capable of inducing a therapeutic or protective immune response

of the appropriate specificity, titer, and duration. The disclosure fails to identify those molecular determinants that modulate protective CTL responses. Accordingly, the skilled artisan has been extended an undue invitation to guess as to which peptides, formulations, and routes of administration might prove useful.

Applicants further submit that the claimed invention is fully enabled since the art illustrates that HIV-1 peptides can induce CD8+ immune responses. As set forth *supra*, simply generating an HIV-1-specific CTL response does not mean that said response will be therapeutic or prophylactic. A declaration by Dr. Franchini was also provided in support of this argument. Dr. Franchini indicated that preliminary results have been obtained from a clinical trial involving ACTG5054 which is an ALVAC recombinant encoding Gag, PR, and Env. Applicants noted that a reduction in viral load was observed in this study. Applicants are reminded that the claims are not directed toward any particular expression vector or CTL epitope. Considering the unpredictability of the prior art, a single example would be insufficient to enable the full breadth of the claimed invention. Applicants may wish to amend the claim language to reference those particular constructs wherein positive results have been obtained. Applicants may also wish to amend the claim language to specify that an immunogenic composition (as opposed to a vaccine) comprising a recombinant ALVAC:X (CTL epitope) is administered wherein said recombinant induces an HIV-1-specific CTL response and lowers the viral burden.

Applicants also reference a press release by EuroVacc and articles by Jin et al. (2002) and Smith et al. (2005). The EuroVacc press release is not terribly informative since it fails to provide a detailed accounting of the actual peptides

employed, those CTL epitopes that are protective, and the specificity, duration, and magnitude of the immune response. Simply identifying a CD8⁺ immune response does not mean that said response will be therapeutic or protective. Concerning the Jin et al. (2002) and Smith et al. (2005) publications, applicants are reminded that in order to overcome a *prima facie* case for lack of enablement, applicants must demonstrate that the disclosure was enabled as of the filing of the application (see M.P.E.P. § 2164.05(a)). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.2d 1123, 1128, 190 U.S.P.Q. 402, 405-06 (C.C.P.A. 1976). *In re Budnick*, 537 F.2d 535, 538, 190 U.S.P.Q. 422, 424 (C.C.P.A. 1976). The effective filing date of the instant application appears to be 28 July, 1999. However, the publications relied upon were published well after this date. Moreover, the Smith et al. (2005) study involved a macaque model that is not reasonably predictive of human vaccine development. The Jin et al. (2002) publication is also less than persuasive. The authors themselves concluded (p. 2214, last paragraph) that "Although the ALVAC vCP1452 plus rgp160 regimen can induce both humoral and cellular immune responses in HIV-1-infected individuals on HAART, the limited magnitude of the CD8⁺ T-cell response and the lack of persistence of T helper cell responses may limit the utility of this particular immunogen in this clinical setting." Accordingly, the rejection is proper and hereby maintained.

Finality of Office Action

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

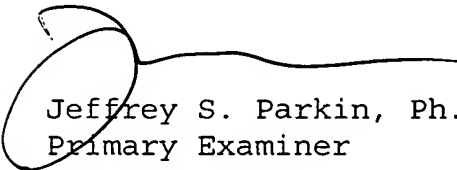
Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, James C. Housel, can be reached at (571) 272-0902. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,



Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

20 August, 2005